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TRANSDERMAL THERAPEUTICALLY ACTIVE PHARMACEUTICAL COMPOSITION AS WELL AS MEANS FOR ITS APPLICATION

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Description

The invention concerns itself with a transdermal, therapeutically active pharmaceutical composition with a film-forming polymer containing the active material, as well as a carrier matrix for the transdermal, therapeutic composition and the application of that carrier matrix.

Such compositions are also frequently described as transdermal therapeutic systems for medically active substances. Systems of this kind are used for a continuous, metered delivery of medical substances, like e.g., nitroglycerin, to a blood system. Various types of the systems of this kind are known. They have in general a microporous plastic container containing the active ingredient. It can be covered on the side contacting the skin by a microporous membrane with a lower permeability for the active substance than that of the container and, accordingly, it plays a role of a control membrane metering the active material. In another familiar type of a system, the active substance is contained in porous microcapsules embedded in a pressure sensitive adhesive and applied directly to the skin. Further, there are systems of transdermal application of medications in which the active material is transferred to the skin from a plastic matrix through a transfer layer in which the medicament has certain saturation solubility. In this case, metering of the medication is controlled by the saturation solubility of the active substance in the transfer layer.

Moreover, there are film-forming polymers in aerosols used as wound spray or for the treatment of local conditions. Such film-forming compositions can contain antimicrobial or locally active substances. These systems are, however, not exactly metered on a predetermined skin area targeted for resorption and don't aim to control the release of the active material from the system and through the skin. Therefore, medication cannot act in a systemically controlled way over a longer period of time delivering a constant plasma level.

The invention aims to create a transdermal, therapeutically active pharmaceutical composition of the above mentioned kind giving a possibility of reaching a predetermined plasma level over longer time periods, especially over the period of at least 12 hours, and keeping it constant throughout this time. A further goal of the invention is to secure the effect without the application of traditional covers and other inconvenient in handling accessories. In particular, the invented pharmaceutical composition should simplify the application and, therefore, correct treatment. The solution of the problem by the invented transdermal therapeutic pharmaceutical composition consists primarily in the fact that transdermal therapeutically active composition contains

a. a polymer liquid matrix curing to form a flexible film, consisting of a vinylpyrrolidone-vinylacetate copolymer and a butyl ester of the polymethacrylic acid,
b. the active substance
c. the release of the active substance controlling solvent, in which the active substance is partially or completely soluble, wherein the solvent is selected from the group consisting of sorbitan macrogollaurate, paraffin, diglycerides or triglycerides of fatty acids with a medium chain length, propylene carbonate or mixtures thereof, and
d. a solvent for the matrix evaporating on the skin present together with a propellant in a device for metered spraying of the composition onto a predetermined area.

Thanks to the fact that the composition contains solvent controlling the delivery of the active substance and the active substance is at least partially soluble in the solvent and both are contained in the polymer liquid matrix which is curing to a flexible solid matrix, the use of additional membranes and application of covers can be eliminated. An advantageous polymer liquid matrix consists of a vinylpyrrolidone-vinylacetate copolymer and a butyl ester of the polymethacrylic acid. Such matrix can be washed by water and se-

cures sufficient wear stability and mechanical strength of the flexible film after curing. As a solvent, or solvent mixture, controlling the release of the active substance and in which the active substance is partially soluble, first of all sorbitan macrogollaurate, paraffin, medium-chain fatty acid di- and triglycerides, propylene carbonate or mixtures thereof can be considered. Due to the matrix solvent evaporating on the skin, the curing to a flexible film is accelerated. Due to the fact that the composition is formulated so that it can be present together with a propellant in a device for a metered spraying, the handling and application are significantly simplified and also the device for metered spraying accurately targets the predetermined application area. At the same time, transdermal system control prevents excessive active substance concentrations, since depending on the predetermined area and dosage, the maximum acceptable concentrations of the active substance in the blood is securely assured and kept constant over a long period of time.

It is advantageous to have vinylpyrrolidone-vinylacetate copolymer and a butyl ester of the polymethacrylic acid in a mix ratio of 3 : 1 to 1 : 3. In a particularly advantageous configuration, the mixing ratio of vinylpyrrolidone-vinylacetate copolymer and a butyl ester of the polymethacrylic acid should be 1.3 : 1 to 1 : 1.3, whereby with increasing portion of butyl ester of polymethacrylic acid the films formed on the skin can be easily pulled off.

The addition of the butyl ester of polymethacrylic acid to vinylpyrrolidone-vinylacetate copolymer in the above mentioned quantity ratios serves first of all the purpose of achieving a sufficient resistance to abrasion. In principle, also other polymers, like for example shellac, eudragite or HPMCP are suitable, however, due to the addition of a propellant, an attention should be paid to preventing polymer additives precipitating from the solution. An additional limitation in using such polymer additives results from the requirement that the orifice of the spray head should not be clogged. Especially, the application of ethyl cellulose didn't succeed for this reason for ethyl cellulose has a tendency to clog the orifice of the spray head.

There are many active substances, for which a continuous delivery would be desirable. In particular, active substances permeating through the skin, showing strong physiological effects at low plasma levels and having low biological half value times, as for example nitroglycerin, are especially advantageous in applications within the framework of the invented pharmaceutical composition. In addition, however, such active substances can be used as medication against motion sickness, like tropic acid ester or scopolamine, beta blocker like propanolol, migraine medication like methysergid, antihypertonics like clonidine and reserpine, hormones like estradiol, analgesics like fentanyl, aspirin, ibuprofen, piroxicam and phenylbutazone, local anesthetics like procaine and lidocaine, calcium antagonists and heart-blood system agents like nifedipine, nicardipine and molsidomine, sedatives like phenobarbital and cyclobarbital but also nicotine, antitumor agents like crestine and ancitabin, enzymes like lysozyme. In case of nitroglycerin as an active substance, an advantageous method is to use nitroglycerin as a 10% alcohol solution or solution in fatty acid di- and triglycerides or mixtures thereof dissolved in the composition.

Particularly suitable values of a desired plasma level can be reached especially by the ratio of 2 : 1 to 1 : 2 of the active substance to the solvent or a mixture of solvents controlling the release of the active substance. In an especially advantageous way, the ratio of the active substance to the solvent controlling the release of the active substance should be 1 : 1 to 1 : 1.5.

To secure rapid drying of the film after spraying on the skin, the solvents with a low boiling point should be selected. Such solvents can come from the group of dichloromethane, ethanol, ethylacetate, isopropanol or mixtures thereof, whereby especially the

use of ethylacetate improves the spraying behavior due to elimination of squirting. Ethylacetate forms particularly homogeneous films on the skin.

Any volatile organic compound with a boiling point below 7°C and inert relative to the possible additives in the composition may be used as propellant in the invented composition. For example, they can be hydrocarbons, propane, butane, isobutane, halogenated hydrocarbons, fluorochlorohydrocarbons, like dichloro-difluoromethane, as well as dimethylether, as well as their mixtures.

Considering the above mentioned limitations in application of the components of the polymer matrix with a simultaneous presence of a propellant, advantageous ratio of polymer matrix to solvent and propellant should be within the range from 1 : 10 to 1 : 15. In an especially advantageous realization, the ratio of polymer matrix to solvent and propellant should be between 1 : 11 and 1 : 13. Keeping such quantity ratio prevents clogging of the spray can by the fast hardening polymer particles or its partial blockage. It is important primarily due to the fact that with a just partially blocked spray can, no homogeneous film can be formed over the entire sprayed surface.

Particularly, application of sorbitan macrogollaurate, as a solvent controlling the release of the active substance, has here an advantageous side effect in that the selection of a suitable quantity of this solvent permits the adjustment of the flow in a wide range of outputs.

To secure a good hardening of the composition and a flexible solid matrix, the advantageous quantity of the solvent or solvent mixture controlling the release of the active substance in the pharmaceutical composition should be maximum 35% in relation to the liquid polymer. Keeping such quantities of the solvent or solvent mixture controlling the release of the active material relative to polymer components guarantees that the pharmaceutical composition forms a non-sticking and abrasion resistant film.

The invented transdermal therapeutic composition contains preferably 2 to 10% of polymer components curing to a flexible film, 15 to 50% of a solvent with a low boiling point, 0.5 to 5% of a solvent or solvent mixture controlling the release of the active substance and 50 to 80% of the propellant as well as an active material.

The invented pharmaceutical composition can be manufactured in a particularly simple way, since only the components should be mixed in corresponding quantity ratios and the transdermal therapeutic composition will be created after the targeted application on the skin by evaporation of volatile solvents and formation of a film. This manufacturing process differs from the known manufacturing processes for transdermal therapeutic systems in that it doesn't require any elaborate technical preparation of the system.

Altogether, application of the invented composition in the form of a spray or aerosol results in a particularly simple manufacturing and better compatibility in comparison to known transdermal therapeutic systems, because the film remains on the skin and requires no special covering, can be produced extremely thin and, therefore, doesn't adversely affect the breathing of the skin and, especially, barely influences gas and water exchange with the surroundings. Based on the thin film, also heat gradient is lower as compared with the known systems resulting in a significantly greater subjective comfort compared with thick and heavy plasters. Moreover, the polymer flexible film can be made transparent so that it would be not immediately recognizable. The rapidly evaporating solvents of the polymer film act before their evaporation as penetration amplifiers resulting in a faster active substance build up after application.

Considered the simplicity of the application, also individual metering is entirely possible, because to ease the dosage the number of spray strokes could be changed before the desired time periods in each case. The application of the invented polymer matrix

also permits an easy removal of the film without a residue, for example using lukewarm water or pulling the film off.

To a considerable degree, the carrier matrix of the transdermal therapeutic composition is characterized by the content of curing to a flexible film, polymer components like vinylpyrrolidone-vinylacetate copolymers and butyl ester of polymethacrylic acid, a solvent or solvent mixture controlling the release of the active material contained in the composition and selected from the group of sorbitan macrogollaurate, paraffin, medium chain di- or triglycerides of fatty acids, propylene carbonate or mixtures thereof, and fast evaporating, film formation promoting solvent selected from the group of ethanol, dichloromethane, ethylacetate, isopropanol or mixtures thereof, and also contains 2 to 10% of polymer components curing to a flexible solid film, 15 to 50% of a solvent with a low boiling point, 0.5 to 5% of a solvent or solvent mixture controlling the release of the active substance and 50 to 80% of a propellant. Such carrier matrix is particularly suitable for application in a preferable way in the manufacturing of a transdermal therapeutic pharmaceutics. The invented carrier matrix creates after the application to the skin a particularly rapidly curing homogeneous film that cannot be removed from the skin by rubbing. The flexible film formed from the carrier matrix can be, however, easily removed using lukewarm water or directly pulled off.

The invention will be explained in more detail based on the following exemplary embodiments.

Example 1:

In a brown glass bottle furnished with a 300 mg metering valve, an aerosol of the following composition was made:

10% ethanol nitroglycerin solution	40.0 mg
Butyl ester of polymethacrylic acid (MW: 100,000)	11.0 mg
Vinylpyrrolidone-vinylacetate copolymer (MW: 50,000)	10.0 mg
Ethanol	5.0 mg
Methylene chloride	38.0 mg
Sorbitan macrogollaurate	5.0 mg
Propellant	191.0 mg
	300.0 mg

Obtained aerosol of this composition had good spraying properties and formed a uniform film on the skin. The film could not be removed by rubbing, but was easily removed using warm water (~35°C).

Example 2:

In a brown glass bottle furnished with a 300 mg metering valve, an aerosol of the following composition was made:

10% ethanol nitroglycerin solution	40.0 mg
Butyl ester of polymethacrylic acid (MW: 100,000)	11.0 mg
Vinylpyrrolidone-vinylacetate copolymer (MW: 50,000)	10.0 mg
Ethanol	5.0 mg
Methylene chloride	38.0 mg
Medium chain di- or triglycerides of fatty acids	5.0 mg
Propellant	191.0 mg
	295.0 mg[1]

Obtained aerosol of this composition had good spraying properties and formed a uniform film on the skin. The film could not be removed by rubbing, but was easily removed using warm water (~35°C).

Example 3:

In a brown glass bottle furnished with a 300 mg metering valve, an aerosol of the following composition was made:

10% ethanol nitroglycerin solution	40.0 mg
Butyl ester of polymethacrylic acid (MW: 100,000)	11.0 mg
Vinylpyrrolidone-vinylacetate copolymer (MW: 50,000)	10.0 mg
Ethanol	5.0 mg
Methylene chloride	38.0 mg
Propellant	191.0 mg
	300.0 mg[2]

Obtained aerosol of this composition had good spraying properties and formed a uniform film on the skin. The film could not be removed by rubbing, but was easily removed using warm water (~35°C).

Example 4:

In a brown glass bottle furnished with a 300 mg metering valve, an aerosol of the following composition was made:

10% ethanol nitroglycerin solution	40.0 mg
Butyl ester of polymethacrylic acid (MW: 100,000)	11.0 mg

[1] it seems authors erred in addition; it should be 300.0 mg (translator)
[2] the total here should be 195.0 mg

Vinylpyrrolidone-vinylacetate copolymer (MW: 50,000)	10.0 mg
Ethanol	5.0 mg
Methylene chloride	38.0 mg
Paraffin	5.0 mg
Propellant	191.0 mg
	300.0 mg

Obtained aerosol of this composition had good spraying properties and formed a uniform film on the skin. The film could not be removed by rubbing, but was easily removed using warm water (~35°C).

Example 5:

In a brown glass bottle furnished with a 300 mg metering valve, an aerosol of the following composition was made:

10% ethanol nitroglycerin solution	40.0 mg
Butyl ester of polymethacrylic acid (MW: 100,000)	11.0 mg
Vinylpyrrolidone-vinylacetate copolymer (MW: 50,000)	10.0 mg
Ethanol	5.0 mg
Methylene chloride	38.0 mg
Ethylacetate	38.0 mg
Sorbitan macrogollaurate	5.0 mg
Propellant	161.0 mg
	300.0 mg

Obtained aerosol of this composition had good spraying properties and formed a uniform film on the skin. The film could not be removed by rubbing, but was easily removed using warm water (~35°C).

Example 6:

In a brown glass bottle furnished with a 300 mg metering valve, an aerosol of the following composition was made:

10% ethanol nitroglycerin solution	80.0 mg
Butyl ester of polymethacrylic acid (MW: 100,000)	11.0 mg
Vinylpyrrolidone-vinylacetate copolymer (MW: 50,000)	10.0 mg
Ethanol	5.0 mg

Methylene chloride	38.0 mg
Ethylacetate	30.0 mg
Sorbitan macrogollaurate	5.0 mg
Propellant	121.0 mg
	300.0 mg

Obtained aerosol of this composition had good spraying properties and formed a uniform film on the skin. The film could not be removed by rubbing, but was easily removed using warm water (~35°C).

Example 7:

In a brown glass bottle furnished with a 300 mg metering valve, an aerosol of the following composition was made:

10% ethanol nitroglycerin solution	40.0 mg
Butyl ester of polymethacrylic acid (MW: 100,000)	16.0 mg
Vinylpyrrolidone-vinylacetate copolymer (MW: 50,000)	5.0 mg
Ethanol	5.0 mg
Methylene chloride	38.0 mg
Ethylacetate	30.0 mg
Sorbitan macrogollaurate	5.0 mg
Propellant	161.0 mg
	300.0 mg

Obtained aerosol of this composition had good spraying properties and formed a uniform film on the skin. The film could not be removed by rubbing, but was easily removed using warm water (~35°C) or directly pulled off.

Using the recipe from example 1, a resorption test was performed on volunteers and the flow of the active substance determined after 3, 6, 9 and 12 hours. To do this, a spray stroke of 150 mg, containing 2 mg of the active material was sprayed on the aluminum foil. The sprayed surface area was exactly 5 cm^2. After drying of the film, the foil was weighed with the film and subsequently half of the foil put on the skin. The content of the active substance was determined from the second half of the foil. After 3 hours, the first half of the foil was removed from the skin and the quantity of the absorbed active substance determined. After that, similar tests were performed for the periods of 6, 9 and 12 hours. From the absorbed quantity of the active substance, the flow of nitroglycerin through the skin can be determined.

The resorption test has shown the following results:

Time	Active material flow
3 hours	11.9 µg/cm²/hr
6 hours	11.4 µg/cm²/hr
9 hours	12.6 µg/cm²/hr
12 hours	7.5 µg/cm²/hr

The flow of the therapeutically active substance should be on the order of 15 to 25 µg/cm²/hr. The flow of the active substance of this order of magnitude ensures a sufficient plasma concentration of the active ingredient on a covered area of 10 cm². The values found in the described resorption test were entirely under the desired values but were very constant over the time of at least 9 hours. However, since the active composition was coated on the surface area of 5 cm², it is easy to see that by coating of four spray cans on a surface of 5 cm² each an effective range of the plasma level can be reached. Also, the clearly lower value for the active substance after 12 hours can be explained by the smaller quantities of the active substance on the skin of the volunteer testers, because the active material reserve was used down to about 60% at that time. A constant active material flow for a period of up to 24 hours was not the goal of this experiment, because nitroglycerin as an active substance is subject to a tolerance development and, therefore, the composition looses its therapeutic effectiveness with the time, so that a dose reduction, for example during the night time, seems to be desirable.

Further increase of the flow of the active substance during the saturation phase can be surely reached when the pharmaceutical composition is sprayed directly on the skin.

In a second resorption test on the volunteers, pharmaceutical compositions according to the examples 1 through 4 were sprayed and applied in the just described way. After 6 hours, the first half was removed and the absorbed active material quantity determined. Active material flow can be determined from the absorbed active material quantity. Herein, recipe from example 1 reached a flow of 11.83 µg/cm²/hr and recipe according to example 2 a flow of 15.7 µg/cm²/hr, recipe according to example 3 a flow of 3.52 µg/cm²/hr and the recipe according to example 4 resulted in a flow of 7.1 µg/cm²/hr. Since also in these tests only a spray stroke on the surface area of 5 cm² was shot and in the stroke contained only about 2 mg of the substance, the doubling to quadrupling of the surface area sprayed with the composition a therapeutically effective plasma concentration can be reached. It is especially valid for the recipes 1 and 2, whereby the recipes according to the examples 3 and 4 would not reach therapeutically effective range of the plasma level even by quadrupling the surface area sprayed with the composition and, therefore, quadrupling of the active material quantity.

It can be seen from these results that a desired control of the active material flow can be attained by using various solvents. Particularly suitable solvents controlling the release of the active material are sorbitan macrogollaurate and the medium-chain di- and/or triglycerides of fatty acids, contained in the recipes of the example 1 and 2. Paraffin used in example 4 secures only about a half of the value of the active material flow, and the values achieved without such solvents controlling the release of the active material, lie in the range of 3.5 µg/cm²/hr and, hence, far below the therapeutically applicable flow.